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## **Melanoma occurring during treatment with fingolimod for multiple sclerosis: A case report**

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### **Key words**

Melanoma, immunogenicity, immunomodulation, fingolimod, FTY720, multiple sclerosis

**Abbreviations**

Fingolimod: FTY720

Multiple sclerosis: MS

Malignant Melanoma: MM

Relapsing-remitting multiple sclerosis: RRMS

Sphingosine-1-phosphate: S1P

Squamous cell carcinoma of the skin: SCC

## Introduction

Recently, immunomodulation rather than simple immunosuppression has proven beneficial in the treatment of Multiple Sclerosis <sup>1-4</sup>. Novel, effective immunomodulating agents such as fingolimod (FTY720) are expected to be launched in the near future. As far as published (ref), efficacy and safety of fingolimod are very promising (ref). To obtain long-term safety data, a close follow-up of patients treated with new immunomodulating agents and publication of newly detected relevant side effects and risks is warranted.

As a functional sphingosine 1-phosphate receptor antagonist, FTY720 inhibits lymphocyte emigration from lymphoid organs, thereby acting as an immunomodulator <sup>5</sup>. The results of clinical studies investigating FTY720 for the treatment of MS are promising <sup>1</sup>. The development of neoplasms has been discussed as a potential risk. Large phase II and III studies did not show a significant risk of the development of certain types of cancer during the time period of observation <sup>1, 6</sup>. However, the Phase II clinical study with FTY720 in MS showed a higher than expected rate of skin malignancies (basal cell carcinoma, squamous cell carcinoma and melanoma) <sup>1, 7-8</sup>. As a consequence of such observations, annual dermatological full-skin examinations have been integrated into the clinical phase III trials for FTY720 in MS; however after recruitment was complete and therefore without baseline exam. The published data of the phase III TRANSFORMS trial for short-term application of FTY720 showed no melanoma in 420 patients on 1.25 mg FTY720, three melanomas in 429 patients on 0.5 mg FTY720, and no melanoma in 431 patients on interferon beta-1a. <sup>9</sup>. In the phase III FREEDOMS trial <sup>10</sup> with patients treated with FTY720 over 24 months, one melanoma in 429 patients on 1.25 mg FTY720, no melanoma in 425 patients on 0.5 mg FTY720, and one melanoma in 418 patients on placebo were noted. The only recently published 3- year results of a phase II study showed one patient with MM in the placebo/ FTY720 group after 25 months and one patient with MM in the FTY720 1.25 mg group after 36 months. Following this 36 months analysis no additional skin cancers were detected during months 36-48 <sup>8</sup>. However, no data are available yet concerning possible risks for continued treatment beyond the observed timeframe <sup>8</sup>. Here, we present the case of a MS patient who was diagnosed with melanoma after months 4 years of FTY720 (1.25 mg) continued use by dermatological full-skin examination and discuss the potential underlying mechanisms and consequences. This represents the first melanoma case occurring under long-term treatment with FTY720.



## Case report

A 41- year- old Caucasian female was diagnosed with relapsing-remitting multiple sclerosis (RRMS, MS) after experiencing intermittent hypaesthesia of the right hand in February 2002 and intermittent ataxia of the left leg and right hand in April 2003 <sup>11</sup>. MRI of the head in 2002 showed multiple periventricular, juxtacortical and infratentorial, T2 hyperintensive lesions, and cerebral MRI in 2003 showed a new T2 lesion in the right thalamus. Analysis of the cerebrospinal fluid in 2002 showed 10 cells/ $\mu$ l, oligoclonal bands and an elevated IgG index of 1.8. Diagnosis of RRMS was made, and after providing informed consent the patient was enrolled in a double-blind, randomized, placebo-controlled, parallel group, multicenter study evaluating safety, tolerability and effect on MRI lesion parameters of FTY720 vs placebo in patients with RRMS (CFTY720D2201) in January 2004. She had been allotted placebo from January 2004 to September 2004 in the core trial. In September 2004 the treatment was switched to the active compound FTY720 1.25 mg p.o./d continuously in the extension phase of the study CFTY720D2201 (FTY720D2201E1). After the start of FTY720 treatment in September 2004, the patient had no further relapses and had no progression of neurological symptoms. MRI studies in April 2008, April 2009 and June 2009 showed multiple inactive plaques consistent with MS, which were unchanged from earlier imaging studies. Apart from FTY720, the patient was on oral contraception with 0.15 mg Desogestrel und 0.03 mg Ethinylestradiol /d. The remainder of her medical history was unremarkable.

Gelöscht: ; FREEDOMS

Gelöscht: C

On annual dermatological whole skin examination in May 2009 after 57 months of 1.25mg/d FTY720 treatment, this patient with a skin type II, less than 50 nevi, no freckles and no signs of sun-damaged skin presented with an asymmetrical, irregularly pigmented macule of about 5 mm on the left paravertebral dorsum with central hypopigmentation and irregular borders (figure 1 - 2). This lesion had not been noted on dermatological examinations in the years before. On dermoscopy, the lesion showed an atypical network pattern with irregularly distributed brown globules and an unspecific pattern in the centre with a hypopigmented whitish-red zone. The atypical melanocytic lesion was excised completely. Histological examination showed a melanoma ex naevo with a Breslow thickness of 0.9 mm (figure 3a and 3b) without ulceration. S-100 serum protein as a tumour marker was within normal limits. Further work-up, including chest-x- ray and ultra sound examination of lymph nodes and abdomen, yielded no pathological findings. Treatment with FTY720 was stopped. A wide excision with a security margin of 1 cm was performed. Because of clinical signs of regression in spite of a Breslow

<1 mm a sentinel lymph node biopsy was performed as an exception to routinely followed Swiss guidelines<sup>12</sup>. The sentinel lymph node showed a small intracapsular melanocytic naevus but no evidence of lymph node metastasis on histological examination.

## Discussion

### *FTY720 is a functional sphingosine 1-phosphate receptor antagonist*

Briefly, sphingosine-1-phosphate (S1P) as a lysophospholipid regulates numerous functions in intra- and extracellular compartments. Best known are effects on the cardiovascular and the immune system. Five sphingosine 1-phosphate receptors are known (S1P<sub>1</sub> to S1P<sub>5</sub>). Phosphorylated FTY720 binds and activates S1P<sub>1</sub>, S1P<sub>3-5</sub>, but not S1P<sub>2</sub><sup>13</sup>. While FTY720 is an agonist at these four S1P receptors, its binding leads to internalization and loss of receptor surface expression. FTY720 intriguingly ends up being a functional S1P antagonist with inhibition of lymphocyte egress from lymph nodes and secondary lymphoid tissues<sup>14</sup>. These properties have led to FTY720 being developed as a promising immunomodulatory drug in multiple sclerosis (MS)<sup>1</sup>.

### *Extended clinical trials provide new data on FTY720 in MS*

The results from ongoing clinical MS trials are encouraging. However the continued use of FTY720 has been connected with a higher than expected rate of skin malignancies in the phase II study<sup>8</sup>. The reported short-term phase II data of continued treatment up to 36 months did not show a relevant elevation of this incidence<sup>7, 10</sup>. Our observed case of melanoma represents a melanoma occurring during extended treatment with FTY720 beyond the hitherto reported timeframe. While data on the role of S1P in melanoma formation is patchy, direct and indirect effects of S1P receptor modulation may matter for melanoma formation.

### *Direct effects of sphingosine 1-phosphate receptor modulation on melanoma*

Sphingolipids have long been considered as rather passive structural components of cellular membranes. More recently, it has become evident that metabolism of sphingomyelin yields several lipid mediators that evoke diverse and specific responses in different cell types. The sphingomyelin derivate S1P has attracted particular attention in the interactions with malignant cells. S1P signalling has been linked with complex effects on several types of carcinoma cells via regulating migratory responses in epithelial tumours<sup>15-16</sup>. Davaille et al.<sup>17</sup> suggested a concentration-dependent effect of S1P for survival and apoptosis in human hepatic myofibroblasts.

For melanocytes and melanoma cells, S1P exerts an influence which seems highly dependent on the receptor subtypes involved. S1P protects mouse melanocytes from UVB induced apoptosis by



phosphorylation of both ERK and Akt and thus promotes survival<sup>18</sup>. The migration of B16 murine melanoma cells could be manipulated by S1P receptor subtype expression. Mainly, S1P<sub>2</sub>, for which FTY720 is not a ligand, downregulated cell motility and invasion, while agonism at S1P<sub>1</sub> and S1P<sub>3</sub> led to B16 migration<sup>19</sup>. Furthermore, S1P<sub>2</sub> activation inhibited melanoma metastasis formation in a murine model, while S1P<sub>1</sub> activation aggravated metastasis in this model<sup>20</sup>. The balance between ceramide and S1P expression was found to be critical for apoptosis susceptibility in human melanoma cell lines in culture<sup>21</sup>. Inhibition of angiogenesis and tumour vascularisation was shown for FTY720 with inhibited metastatic melanoma growth in a mouse model via decreased tumour cell proliferation and increased apoptosis<sup>22</sup>. S1P can also induce apoptosis in B16 melanoma cells apparently independent of S1P<sub>1-3</sub> receptors<sup>23</sup>. Due to its peculiar properties, FTY720 acts as an agonist of S1P receptors, but yields functional antagonism. Its impact on mechanisms involved in melanoma formation and progression remains elusive at this point in time.

#### *Indirect effects of sphingosine 1-phosphate receptor modulation on melanoma*

Melanoma as neoplasm is in close contact with the immune system. Clinical signs include the spontaneous regression of primary melanoma and the development of vitiligo and halo nevi in mainly metastatic disease. In-depth analysis of the interplay between melanoma and the immune system over the last two decades has yielded a great number of mostly T-cell specific antigens. Many of these antigens have been applied in the context of clinical immunotherapy trials. While not successful in prolonging survival of patients with metastatic melanoma yet, these trials have demonstrated a clear induction of basic immune reactions with e.g. expansion of melanoma-specific T-cells clones against melanoma antigens<sup>24</sup>.

The risks of immunomodifying treatment in MS have been recognized. Natalizumab is another immunomodulatory agent applied against MS. Observed malignancies include lung, bladder, breast, colon cancer and melanoma with an overall rate of 0.6% in the natalizumab group vs. 0.2% in the placebo group in a short-term, placebo-controlled trial for patients with active Crohn's disease<sup>25</sup>. Association of MM and treatment with natalizumab was recently discussed controversially<sup>26-28</sup>. In a larger context, immunomodulation is under consideration to increase cancer incidence in several disease conditions<sup>29-32</sup>.

**Kommentar [GH1]:** Ist aus meiner Sicht wichtig, würde ich lieber nicht weglassen. Müssen GH und ML besprechen.

## Conclusions

We describe a case of melanoma development during long-term treatment with FTY720. Causality is speculative. However, due to possible interactions between melanoma formation and progression with S1P and its receptor subtypes, FTY720 may be of functional relevance for melanoma formation.

Currently, it is not clear whether the higher than expected rate of skin malignancies in MS patients on

FTY720 indeed exceeds the one in the general population. Ongoing clinical trials with FTY720 now include an annual dermatological whole-body skin examination. The incidence reported in the Phase III studies is based on active screening via dermatological exam and is therefore difficult to compare to historic cohorts.

A positive family history is a known risk factor for melanoma<sup>33-34</sup> and should be weighed cautiously in the decision to start FTY720, while a personal history or the occurrence of melanoma should lead to cessation of FTY720 as done in our patient. Until further long-term data emerges to better assess the risk of skin-cancer development during treatment with FTY720, self-examinations of the skin every three months and a dermatological full-skin examination annually may be the best strategy regarding the currently unknown long-term risk of melanoma in FTY720-treated patients. Early removal of melanoma is the only curative treatment for this neoplasm to date.

**Kommentar [ML2]:** ist ein ganz wichtiger punkt, kann man so aber nicht schreiben: entweder es war signifikant, dann übersteigt es die Kontrollgruppe, oder nicht; (testwerte/ p zeigen). Gesamtbevölkerung kann dann wegbleiben.

GH Wird von Novartis selbst so berichtet und formuliert. Signifikanzberechnungen finden hier keine Anwendung. Würde ich daher so belassen, müssen GH und ML besprechen.

**Gelöscht:** control group or the one in the

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